REMARKS

Reconsideration of the application is respectfully requested. Claims 4-11 are pending in the application. Claims 4, 8, and 11 have been amended to clarify the claimed invention.

It is believed that the present amendments are in compliance with 37 C.F.R. § 1.116 since no new searching is necessary, and the amendments are believed to place the claims in condition for allowance. No new matter is added by way of these amendments. Claims 4-11 are pending and at issue.

Rejections under 35 U.S.C § 112, first paragraph

The Examiner has maintained the rejection of claims 4-11 under 35 U.S.C § 112, first paragraph, as lacking enablement. The Examiner states that the specification does not reasonably provide enablement for: 1) a method of treating cancer *in vivo*; and 2) the use of the claimed nucleic acid wherein the E1 gene is not operably linked to a promoter to cause expression (*see* Office Action, page 3-4). The Examiner concedes that the specification is enabling for a method of causing cytotoxicity in cancer cells comprising injection, *in vitro* or *in situ*, of a vector into a tumor comprising said cancer cells, the vector comprising the hTERT promoter operably linked to a polynucleotide comprising a gene encoding adenovirus E1A gene followed by an IRES, and a gene encoding E1B, as well as being enabling for the nucleic acid itself.

With respect to part 2), claim 4 has been amended to recite that that hTERT promoter is operably linked with E1A gene, an IRES sequence, and an E1B gene. Support for this amendment is found throughout the published specification, for example, at ¶¶ 30, 33, 36, 54, and Figure 1. The Examiner acknowledges that the specification is enabling for this cassette.

With respect to enablement for a method of treating cancer *in vivo*, Applicants initially point out that in contrast to the Examiner's characterization, Example 6 describes the application/administration of a vector (TRAD) construct encompassed by the pending claims to subcutaneously transplanted lung and large bowel cancer cells in nude mice. The anticancer

activity observed in Example 6, compared to a control vector (Ad-p53) that contained no inserted gene (i.e., dl312), is attributable to the injection of a vector encompassed by the claimed methods. The TRAD vector kills cells by replication. In contrast, the control Ad-p53 vector kills cells by expressing the therapeutic gene p53 (*See* Example 6 and Figs. 8-9). In other words, Ad-p53 is a control vector used to compare with TRAD.

Furthermore, the test for enablement "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." *In re Wands,* 858, F.2d 731, 737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (quoting *In re Angstadt*, 537 F.2d 489, 502-4, 190 USPQ 214, 217-19) (CCPA 1976)); MPEP § 2164.01. Applicants submit that as described in detail herein, and as further characterized by the Examiner, Example 6 is a working example wherein vectors containing the claimed cassette were injected into tumors, thereby killing tumor cells. This is an *in vivo* (described by the Examiner as "*in situ*," but a nude mouse is in fact a live animal and an *in vivo* model) example utilizing an exemplary vector construct. Thus, the specification provides adequate guidance for a person of ordinary skill in the art to make and use the claimed invention both *in vitro*, and *in vivo*. Because adequate guidance is provided, the specification enables the pending claims which encompass methods for killing tumor cells utilizing the claimed vector constructs.

Applicants also point out that there are many *in vitro* assays that have been extrapolated for use in human diagnostic assays or treatments. There are many examples of such assays - notably the *in vitro* assays using Tamoxifen® in MCF-7 cells that have been successfully applied not just to human diagnostic methods, but for treatment of human breast cancer. See for example, *Curr. Opin. Obstet. Gynecol.* 2003 Feb;15 (1):13-23 (listed in the Information Disclosure Statement of Feb. 23, 2005), "as a prototype for the development of selective estrogen receptor modulators at the laboratory-clinical interface." (*Id.* at page 13, second full paragraph).

It is also respectfully submitted that, in any event, *in vivo* data using the claimed vectors is not necessary in order to comply with the enablement requirements of 35 U.S. C. § 112, first paragraph. Courts have consistently and repeatedly held that *in vitro* activity is sufficient to satisfy the "how to use" portion of the enablement requirement of U.S. patent law. The Manual of Patent Examining Procedure (MPEP) § 2107.01, quoting *Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir. 1985), states:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

MPEP § 2107.01 further states:

> [C]ourts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition.

Additionally, the Courts have stated that *in vivo* testing is not necessary to satisfy the "how to use" portion of the § 112 enablement requirement. For example, the Court of Appeals for the Federal Circuit has acknowledged that if human testing were required to prove that a compound is useful within the meaning of the patent laws, "the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas ***such as the treatment of cancer.***" *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) (emphasis added).

Finally, MPEP § 2164.02 discusses correlation of *in vitro* and *in vivo* animal model assays and a disclosed or claimed method of use. Importantly, correlation depends upon the state of the prior art in view of whether a particular model is recognized as correlating to a specific condition. If so, a model should be accepted as correlating unless the examiner has evidence that

the model does not correlate. Importantly, MPEP § 2164.02 further states that "even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition." Thus, the nude mouse model for killing tumor cells described in Example 4, and the results of injecting the nude mice with a vector construct, fully enable claims 4-11.

In view of the foregoing remarks, the rejection of these claims under 35 U.S.C.§ 112, first paragraph should be withdrawn.

Rejections under 35 U.S.C § 103

Claims 4, 5-8, and 11 have been rejected under 35 U.S.C § 103 as obvious over Morin et al. (WO 00/46355) ("Morin") in view of Li, et al., *Cancer Res.*, 61(17)6428-6436 (2001) ("Li"). According to the Examiner, it would have been obvious to a person of ordinary skill in the art to combine Morin, which discloses cell and tissue specificity of the hTERT promoter and its transcriptional regulation in an adenovirus, with Li, which discloses a bicistronic cassette in an adenovirus 5 vector (Ad5) that harbors an E1A gene, an IRES sequence, and an E1B arranged in E1A-IRES-E1B order (*see* Office Action, page 14). The Examiner contends that a skilled artisan would be motivated to make the combination because the hTERT promoter taught by Morin activates transcription specifically in tumor cells, and the IRES taught by Li in an Ad5 vector controls the expression of E1A and E1B at the translational level.

For a claim to be obvious under 35 U.S.C. § 103, three criteria must be satisfied: i) there must be some suggestion or motivation to combine or modify the cited references; ii) there must be a reasonable expectation of success of combining or modifying the cited references; and iii) the combined references must teach each and every limitation of the claimed invention. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000). Applicants submit that in contrast to the Examiner's position, there would have been no motivation to alter the teachings of Morin and Li to arrive at the claimed invention and no likelihood of success for killing.

Even if a skilled artisan reading Li decided to replace the AFP TRE with a different promoter, there would have been no reasonable expectation that specifically replacing AFP TRE with hTERT would be successful, or any expectation that such a replacement would produce a cassette "capable of replicating in a tumor cell", particularly in view of the large number of potential promoters that could be utilized in such a system.

At best, the cited references provide only an invitation to experiment further, which is insufficient to establish obviousness in the context of unpredictable results. Determining the various elements that can be combined to make the claimed cassettes was unpredictable until a cassette of that type is made and tested. It was only through experiments carried out by the present inventors as described in the specification, that the parameters for the inventive processes were determined and tested. MPEP § 2145(X)(B); *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988); *see also Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361 (Fed. Cir. 2000) ("'obvious to try' is not the standard").

This conclusion is consistent with the recent Supreme Court decision *KSR v. Teleflex*, 550 U.S.___ (2007)[1] where in contrast to the presently claimed process, the court discussed *predictable* outcomes that support a finding of obviousness stating:

> The combination of familiar elements according to known methods is *likely to be obvious when it does no more than yield predictable results*." (emphasis added) (discussing *United States v. Adams*, 383 U.S. 39, 40 (1966) (the companion case to *Graham*), *Anderson's Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), and *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

Assembling the claimed elements in the manner discovered by the present inventors was not a mere combination that yielded predictable results.

Furthermore, according to the Examiner, a skilled artisan would have been motivated to make the claimed combination because the hTERT promoter taught by Morin activates transcription specifically in tumor (cancer) cells, and the IRES taught by Li in an Ad5 vector

[1] Holding that *Graham v. John Deere* controls the obviousness inquiry and warning that a rigid application of the teaching / suggestion / motivation test as a litmus test for obviousness is inconsistent with the *Graham* framework.

controls E1A and E1B expression at the translational level (*see* Office Action, pages 13-14). According to this argument, then, IRES can drive second gene expression.

Applicants submit this position is not well founded, and that a skilled artisan would not be motivated to make the claimed combination. It is well known in the art that IRES-dependent second gene expression is less efficient than cap-dependent first gene expression. For example, Mizuguchi et al., *Molecular Therapy*, 1(4) (April 2000) ("Mizuguchi") teaches that IRES-dependent second gene expression is less efficient than cap-dependent first gene expression, and also that expression levels of second gene expression can range from 6 to 100 (generally 20-50%) those of the first gene (*see* Mizuguchi, et al., page 378, left column, lines 3-7) (**Attachment A**).

In view of Mizuguchi, a skilled artisan would have understood that the expression of E1B gene under the control of IRES sequence would not be at a sufficient level to cause tumor cell lysis via viral replication. Thus, even if a skilled artisan reading Morin decided to control the expression of E1B at the translational level, there would have been no reasonable expectation that the arrangement of IRES sequence upstream of E1B gene would successfully control the expression of E1B gene at a level sufficient to cause tumor cell lysis by viral replication. Therefore, there would have also been no motivation for doing so, as alleged by the Examiner.

Finally, the claimed polynucleotide cassettes exhibit unexpected and advantageous effects that would not have been predicted by a person of ordinary skill in the art. Specifically, the HCC-specific oncolytic adenoviruses taught by Li replicate ***only in specific types of cancer cells***. In contrast, the claimed virus can be successfully utilized in a variety of different cancer cell types, (e.g., broadly capable of replicating in a tumor cell). Thus, the claimed cassette, broadly capable of replicating in a tumor cell exhibits features not taught by Li and Morin and can be used in the treatment of several different cancer types. The cited references do not teach or suggest such advantageous features.

In view of the foregoing, Applicants respectfully submit that the claimed invention would not have been obvious in view of the cited references. Therefore, the rejection should be withdrawn, accordingly.

CONCLUSION

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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